REMARKS

Claims 1-70 are in the case. Claims 2, 3, 5, 12, 13 and 48-70 are withdrawn from consideration. Claims 1, 4, 6-11 and 14-47 are rejected variousely under 35 USC § 112, 102 and 103.

Claims 1, 4 and 42 have been amended to more clearly define applicants invention

Paragraph numbers below correspond to those in the present action.

No new matter has been added.

Withdrawn Rejections

2. Applicants gratefully acknowledge the withdrawal of the rejections under 35 USC § 112 2d paragraph and the rejections under 35 USC § 102(b).

Claim Rejections – 35 USC § 112

3. Claim 42 is rejected under 35 USC § 112, 2d paragraph for indefiniteness. Specifically the Examiner finds it unclear how a film can prevent non-specific binding and also cause attachment of the capture probe. The Examiner also states that the coating and the film appear to be different entities.

The claim has been amended to overcome this rejection. Support for this is amendment is found on page 41, line 5 to page 42, line 9 of the specification. Additionally, the method is Exemplified in Example 7, Part A and B.

Claim Rejections – 35 USC § 102

Claims 1 and 4 are rejected under 35 USC § 102(e) as being anticipated by Yguerabide, US 2003/0096302, hereinafter "'302".

'302 describes the use of light scattering particles as labels able to identify the presence of an analyte in solution.

The examiner finds that '302 teaches all the elements of the rejected claims. Applicants traverse.

All of the elements of the claims are not found in '302. In particular, with respect to claim 1, '302 does not teach a correlating step as recited in claim 1(e). Additionally '302 does not teach a light scattering system based on detectable shifts in the morphological resonances or structural resonances, and '302 does not teach the use of particles that incorporate a transparent outer optical region which allow for the use of interference of light waves within the particle.

The examiner suggests that par. 0679 and 0684 teach the correlation of the capture probe to a particle by virtue of biotinylation the surface of a gold particle. Applicants understanding of the sequence of events of par. 0679 and 0684 is that 1) a gold particle is bioinylated; 2) a scan of the biotinylated particle is made and resonant light scattering data is

collected; 3) streptavidin is placed on a coverslip; 4) the biotinylated particle is added to the streptavidin coated clover slip; 5) binding occurs between the biotinylated particle and the strepavidin coated coverslip giving rise to a different light scattering profile. The addition of biotin to the particle does not uniquely identify the particle.

With respect to claim 1, each particle is uniquely identified on the basis of a reference light scattering spectrum (part d) and the probe is then correlated with that particle. No such identification is suggested in '302 and no such correlation takes place. Thus, with respect to Claim 1 each and evey element of the claimed invention is not found in the cited reference.

With respect to both Claims 1 and 4 '302 is deficient in teaching the specific light scattering employed and claimed by the invention and the specific particle type used.

The resonance light scattering described by Yguerabide et al. is fundamentally different from the structural resonance light scattering of the instant invention and is a plasmon resonance as opposed to a structural resonance as used ad claimed in the present invention. Yguerabide et al. and the references cited therein teach use of Rayleigh-limit "metal-like" particles (see paragraphs 0283, 0284, 0285, 0307, and many others), taking advantage of the fact that metallic particles with suitable values of the complex refractive index have a much higher scattering cross section than Rayleigh-limit dielectric particles like polystyrene or glass. The high scattering cross section, combined with broad peaks in the scattering spectrum of metallic particles, confers characteristic colors and high levels of sensitivity when used as analyte labels. It is disclosed by Yguerabide et al. and references cited therein that these properties result from Mie scattering theory applied to particles much smaller than the wavelength of light that additionally have suitable values of a complex refractive index (as found in some metals like gold and silver). As disclosed by Yguerabide et al., their labeling techniques are much less effective for dielectric particles (i.e., non-metal-like particles, par 0307, 0376-0383) because of the orders of magnitude lower scattering cross sections for such particles. Stated another way, the resonance light scattering described by Yguerabide et al. is a plasmon resonance wherein optical resonances are formed by coupling light energy of specific wavelengths into electrons of certain metals (e.g., silver and gold). Therefore, the resonance light scattering particles of Yguerabide et al. are limited to certain metal-like particles (paragraph 0235).

In contrast, the instant application discloses a fundamentally different use of resonant Mie scattering which enables the use of dielectric particles. The detection of analyte is not based on total scattering cross section as in the system described by Yguerabide et al. Rather, it is based on detectable shifts in the morphological resonances (also known as structural resonances, page 33, lines 23-27) of the scattering spectrum as analyte is bound to the particle. These resonance are uniquely displayed by dielectric particles of the type disclosed in the instant application and are not displayed in Rayleigh-limit particles of the type disclosed by Yguerabide et al. These structural resonances are due to the interference of light waves within

the particle, not plasmon resonances as described by Yguerabide et al. The light scattered at the resonant wavelengths must be transmitted around the outer optical region of the particle prior to being scattered. Therefore unlike the particles described by Yguerabide et al., the outer optical region of the particles of the instant invention (that part of the core outside the caustic surface) must be substantially transparent at the wavelengths of interest (page 55, lines 13-18). Consequently, the metal-like particles described by Yguerabide et al., which do not have a transparent outer optical region, would not generate the structural resonances of the instant invention because the light waves can not enter the interior of the particles.

The claims have been amended to clearly recite these differences. Basis for the amendments to parts (b) of claims 1 and 4 may be found on page 49 in the paragraph beginning at line 13. Basis for the amendments made to parts (d), (f) and (h) of claims 1 and 4 may be found on page 33, lines 23-27 of the specification.

5. Claims 1, 4, 8, 11, 16-23, 33, 35, and 45-47 are rejected under 35 USC § 102(b) as being anticipated by Hansen et al (US 6200820, "Hansen") in light of Reed US 6618144, "Reed").

The teachings of Hansen has been given previously.

Reed is cited for the teaching of scanning from incident light sources.

The Examiner argues that all of the elements of the claimed invention are found in Hansen in light of Reed. Applicants traverse.

Elements of the invention specifically not taught by Hansen include 1) no teaching of a scan over an analytical wavelength, but rather a teaching of a measurement is made at a constant wavelength; 2) no teaching of a structural resonant light scattering method relying on comparison of light spectrum; 3) no teaching of the identification of a single particle on the basis of a structural resonant light scattering spectrum; and 4) no teaching of a particle having an outer optical region which is substantially transparent to light over the analytical wavelength range.

As pointed out in Applicants' previous response, the method described by Hansen is significantly different than the structural resonant light scattering method of the instant invention. The method described by Hansen is an agglutination light scattering method wherein a first binding molecule-coated microspheres and second binding molecule-coated colloidal particles agglutinate in the presence of the analyte to form a complex. The non-colloidal particles, complexed and non-complexed, are detected using an optical flow particle analyzer in which the particles are counted by the light scatter pulse height caused by the particles passing through a flow cell. The measurement is made at a constant wavelength, i.e., the particles are not scanned over an analytical wavelength range. The light scattering resonances that occur within each particle are not spectrally resolved. Rather, the statistical distribution of the light scattering signals (i.e. pulse heights) for a population of particles, i.e.,

a histogram of the number of events versus the scattered pulse height (see Figures 2B, 2C, and 2D), is determined and correlated with the presence or amount of the analyte.

With respect to the scan over the analytical wavelength; the light source of Hansen produces light at discrete wavelengths and cannot scan over an analytical wavelength range. The Examiner states that since no wavelength range is recited in the Claim 1 of the instant application, an analytical wavelength range encompasses a single wavelength and Hansen scans at single discrete wavelengths. Additionally, as evidenced by Reed, an incident light source taught by Hansen provides a range of wavelengths during an illumination step to obtain a light scattering signature. Applicants respectfully disagree.

One cannot scan at a single discrete wavelength. Scanning means that the wavelength of the light source is varied over an analytical wavelength range (page 27, lines 29 to page 28, line 2) to obtain a structural resonant light scattering spectrum. Scanning is further described on page 32 lines 3-7, page 54 line 30 to page 35, line 1, page 62, line 30 to page 63, line 4, and page 75, line 31 to page 76, line 4 of the instant application. Similarly, one can not obtain a spectrum at a fixed wavelength even if the light source provides a range of wavelengths during illumination. A spectrum is a plot of the scattered light intensity as a function of wavelength (for example, see figures 5, 9, 12, 15, and 18). The difference between scanning and making a measurement at a fixed wavelength can be seen by analogy to uv-vis spectrophotometry. If one takes an absorbance reading at a fixed wavelength, which consists of a range of wavelengths, one obtains a single absorbance reading which is the sum of the absorbances over the range of wavelengths. This is not a scan and it doesn't produce a spectrum. In order to obtain a spectrum, one does a scan over a wavelength range and the absorbance values are recorded and plotted versus the wavelength to obtain a spectrum.

Hansen does not describe obtaining first or second structural resonant light scattering spectrum or comparison of first and second structural resonant light scattering spectra. The Examiner states that claims 1 and 4 do not recite a light source specific for producing resonant light, and therefore, the light scanning source of the instant application encompasses the light source of Hansen. Applicants respectfully disagree. The resonances do not come from the light source; they are generated within the particles, as described above. Also as described above, Hansen does not teach scanning (i.e., varying the wavelength of the light source over an analytical range) each particle one or more times over an analytical wavelength range to obtain a structural light resonant scattering spectrum. The light scattering signature described by Hansen is not a structural resonant light scattering spectrum; in fact, it is not a spectrum at all. It is a plot of the number of events (i.e., number of light pulses detected) versus light scatter pule height (see figures 2B, 2C, and 2D in Hansen). To make this difference more clear, the term "light scattering signatures" has been changed to "light scattering spectrum" in claims 1 and 4. Support for this change can be found on page 21, lines 28-31, page 22, lines 30-33, page 30, lines 14-21, of the specification.

The Examiner states that the resonant phenomenon of the instant application appears to be the same phenomenon as that of Hansen because Hansen teaches the recited steps. Applicants respectfully disagree. As described above Hansen does not teach the steps of scanning (i.e., varying the wavelength of the light source over an analytical range) each resonant light scattering spectrum. Nor does Hansen describe obtaining first or second structural resonant light scattering spectrum or comparison of first and second structural resonant light scattering spectra. The Examiner further states that Hansen obtains the same peak width signatures as that in the instant application recited in Claim 43. Applicants respectfully disagree. The peak widths obtained by Hansen are not peak widths in a resonant light scattering spectrum because Hansen does not obtain a light scattering spectrum, as described above. The peak widths of Hansen relate to the statistical distribution of the light scattering signals (pulses) for a population of particles, i.e., a histogram of the number of events versus the scattered pulse height.

Additionally, Hansen does not describe uniquely identifying each particle and correlating the capture probe with each identified particle. The Examiner states that Applicant does not recite the resonant light scattering signature must be unique for each particle. Therefore, each particle in the class of Hansen is uniquely identified. Furthermore, Hansen teaches producing a unique signature for each particle, which provides unique identification of each particle. Applicants respectfully disagree. In order to unique identify each particle, each particle must have a unique resonant light scattering signature or spectrum otherwise it would not be possible to differentiate one particle from another. In col. 3, line 62-63, Hansen states that individual light scatter signals are produced for each of the non-colloidal particles. The light scatter signal (not signatures) referred to there are pulse heights. Each particle can be detected by a pulse of scattered light as it passes through the detector, but that can not be used to uniquely identify each particle (i.e., differentiate one particle from another). In the method of the instant invention, each particle produces a unique resonant light scattering spectrum that can be used to identify each particle (see figure 5). Claim 1 clearly recites that each particle is uniquely identified, i.e., "(d) scanning each particle of (c) one or more times over a first analytical wavelength range to produce at least one first structural reference resonant light scattering spectrum for each particle of (c), said first structural resonant light scattering spectrum uniquely identifying each particle".

Moreover, the particles described by Hansen does not have an outer optical region which is substantially transparent to light over the analytical wavelength range. The Examiner states that the colloidal particles used by Hansen are substantially transparent to light because they are not detected. Applicants respectfully disagree. The colloidal particles used by Hansen are not detected because they are too small, not because they are transparent. Substantially transparent as defined in the instant application "means that the absorption of

light within the regions of the particle in which structural resonances are produced is sufficiently small so that when the particle is illuminated with light in the analytical wavelength range, the resonances remain observable" (see page 33, lines 23-27 in the specification). It does not mean that the particle is not detectable.

In summary, Applicants submit that each and every element of the claimed invention is not found in Hansen in light of Reed and thus Hansen in light of Reed neither anticipates nor makes obvious the present invention.

Claim Rejections – 35 USC § 103

Claims 6, 7, 9, 10, 14, 15, 24-28, 31, 34, 36-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (US 6,200,820) in light of Reed (US 6,618,144) in view of West (US 6,530,944).

The teachings of Hansen in light of Reed are given above.

West is cited for the teaching that it is possible to scan a particle over an analytical wavelength range to obtain a shift in the wavelength of maximum resonance.

It is the Examiner's opinion that it would have been obvious to one of skill in the art to include in the method of Hansen in light of Reed, the element of scanning a particle over an analytical wavelength range to derive the instant invention. Applicants respectfully traverse.

The discussion above relating to the differences between Hansen in light of Reed and the instant invention are relevant to this rejection and are incorporated here by reference. Regarding claim 6, the Examiner argues that Hansen taken with Reed teach a method of identification of an analyte but fail to teach scanning over an analytical wavelength prior to the attachment of a capture probe, an element supplied by West. Applicants argue that Hansen, would not render the invention obvious to the skilled person because of the additional differences between the method of Hansen in light of Reed and the present invention. The fact that Hansen does not teach the use of a first reference scan to uniquely identify an individual particle (as describe above); that a second scan of each individual particle is not performed to detect binding; that the particles described by Hansen do not have an outer optical region which is substantially transparent to light over the analytical wavelength range; and that the light scattering signature described by Hansen is not a structural resonant light scattering spectrum, would mean that the combination of Hansen in light of Reed, and West could not produce the elements of the claimed invention.

The Examiner states that West teach a particle scanned over the analytical wavelength range prior to applying a capture probe to produce an identifying resonant light scattering signature (surface plasmon resonance). As described above, the structural resonance light scattering of the instant application is not plasmon resonance. The structural resonance of the instant invention are due to the interference of light waves within the particles, not plasmon resonances. Surface plasmon resonance (SPR) is well-known in the art as a label-free

detection system in which optical resonances are formed by coupling light energy of specific wavelengths into the kinetic energy of electrons in a thin film of certain metals on the surface of a prism sensor by total internal reflection. The evanescent light wave samples the region above the sensor, and as a result the resonances shift when analyte molecules are bound. SPR typically requires planar sensors and can be used for microarray detection; however the underlying phenomenon is fundamentally different than disclosed in the instant application in that it ***requires*** use of certain metals on the sensor surface. Specifically, the surface of the sensor does not have a transparent outer optical region, and therefore, would not generate the structural resonances of the instant invention because the light waves can not enter the interior of the sensor. Additionally, the SPR sensor is not a particle and therefore is not capable of generating the optical interferences required for the production of structural resonant light scattering.

The examiner further states that Applicants recite surface plasmon resonance as an analytical method for resonant light scattering signatures. Therefore, the light scattering signatures in the method of West are resonant light scattering. Applicants respectfully traverse. Nowhere in the instant application do Applicants recite that the structural resonant light scattering signatures may be obtained using surface plasmon resonance. As described above, the metal clusters described by West are incapable of generating the structural resonance light scattering of the instant invention. In the instant application, Applicants recite that surface plasmon resonance, as well as other analytical methods (e.g., mass spectroscopy, fluorescence, optical absorbance, and radioactivity) may be used **in combination** with the structural resonance light scattering method of the invention to gain further information (see page 31, lines 11-23) or as an alternative to structural resonance light scattering to identify the particles (page 38, lines 8-13). In the latter case, detection of binding is done using structural resonance light scattering.

The additional teachings of West in respect of claims 7, 14, and 15 (page 6 of the action) Claim 24 (Page 7 of the action); claims 25-28 (page 8 of the action); Claim 27 (page 8 of the action); and Claims 41-44 (page 8 of the action) are moot in view of the deficiencies in the teachings of Hansen in light of Reed.

Amendments made to Claims 1 and 4 herein specify the unique structural resonance requirements of the present invention. In view of these amendments and the above arguments Applicants respectfully request that these rejections be withdrawn.

Claim 29 is rejected under 35 USC § 103 (a) as being unpatentable over Hansen in light of Reed in view of Becker (US2003/0015428), hereinafter "Becker", and further in view of Hayashi (US5124207), hereinafter "Hayashi".

The teachings of Hansen in light of Reed are given above.

Becker is cited for teaching magnetic particles.

Hayashi is cited for teaching magnetic particles comprised of iron oxide.

It is the examiner's view that the skilled person would be motivated to apply the teachings of Becker and Hayashi with respect to magnetic particles to the methods of Hansen to derive the invention as set forth in claim 29. Applicants respectfully traverse.

Applicants' arguments and comments in respect to the rejections under 35 USC § 102 and 103 above are relevant here and are hereby incorporated by reference. Claim 29 includes the limitation of a magnetic particle comprised of iron oxide. Applicants do not dispute that magnetic particles comprised of iron oxide are known however submit that, since Hansen in light of Reed do not teach the limitations of the present invention that the combination of Becker, Hayashi, and Hansen in light of Reed would fail to put the skilled person in possession of the invention.

Claim 30 is rejected under 35 USC § 103(a) as being unpatentable over Hansen in light of Reed in view of Becker.

The teachings of Hansen in light of Reed, and Becker are given above. Becker is additionally cited here as teaching a particle comprising a hollow core.

Claim 30 includes the limitation of a particle comprising a hollow core.

It is the Examiner's opinion that the teaching of Becker with respect to a particle comprising a hollow core, when combined with the method of Hansen in light of Reed would put the invention of Claim 30 in the possession of the person of skill in the art. Applicants respectfully traverse.

As argued above, Hansen in light of Reed in combination with Reed do not teach the elements of the present invention. The teaching of a particle comprising a hollow core is not sufficient to counterbalance the deficiencies in the teaching of Hansen and Reed with respect to the present invention. Thus, Applicants submit that the invention is not obvious in view of the teachings of Hansen, Reed, and Becker.

Claim 32 is rejected under 35 USC § 103(a) as being unpatentable over Hansen in view of Finlan (US 5055265), hereinafter "Finlan".

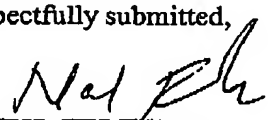
With respect to Claim 32, Hansen in light of Reed is cited for teaching a glass particle used in a method for the identification of an analyte, but fail to teach the index of refraction, whereas Finlan is cited for teaching a glass block having a refractive index of about 2.

It is the Examiner's opinion that the teachings of Hansen in light of Reed when combined with Finlan suggest the claimed invention. Applicants respectfully traverse. The glass block described by Finlan does not possess the structural resonance light scattering properties of the less than 100 μm particles of the instant invention. Therefore, the refractive index of the glass block does not suggest what refractive index would be suitable for use in the structural resonance light scattering method of the instant invention. Additionally,

Applicants again submit that as Hansen in light of Reed does not teach the basic limitations of the present invention that the combination of Hansen in light of Reed and Finlan cannot make the invention obvious to the skilled person.

In view of the foregoing Applicants respectfully request reconsideration of the claims as amended and removal of all rejections.

Respectfully submitted,



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Dated: November 28 , 2005